Microcephalic osteodysplastic primordial dwarfism type II (MOPD II) with multiple vascular complications misdiagnosed as Dubowitz syndrome

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CASE REPORT

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Keywords Microcephalic osteodysplastic primordial dwarfism type II · Dubowitz syndrome · Dwarfism · Vascular · Cerebral aneurysm · Artery

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Abbreviations

MOPD II	Microcephalic osteodysplastic primordial dwarfism type II
MTHFR	Methylene tetra hydro folate reductase
PCNT	Pericentrin

Introduction

Microcephalic osteodysplastic primordial dwarfism type II (MOPD II; OMIM: #210720) is one the most common types of primordial dwarfism and is associated with high childhood and juvenile mortality due to cerebral vessel anomalies, cardiac problems, and early onset type 2 diabetes. As emphasized in a review on pericentrin mutations and beyond by Rauch 2011, the shortest of the short individuals were found to have MOPD II [5]. We report on a 22-year-old man with unexpected cerebral aneurysm bleeding finally diagnosed as MOPD II, who was previously thought and published to have Dubowitz

syndrome (OMIM: %223370) [7] delaying possible interventional treatment.

Case report

The 22-year-old male patient presented with sudden onset of severe headaches followed by a first tonic-clonic seizure. Initial cranial computed tomography (CT) scan with CT angiography revealed extensive intracranial hemorrhage (Fig. 1) resulting from a ruptured aneurysm (size 9×6 mm) of the right proximal internal carotid artery that led to subarachnoid bleeding (SAB). Furthermore, multiple cranial aneurysms (two aneurysms of the right internal carotid artery, one aneurysm of the head of the basilar artery, and one aneurysm of the left posterior inferior cerebellar artery) as well as a moderate narrowing of the left carotid artery were detected. The patient was intubated, ventilated, and admitted to our pediatric intensive care unit.

He had a previous history of myocardial infarction of the anterior wall at the age of 17 years which was treated with triple coronary bypass surgery. At that point, the patient was thought to have Dubowitz syndrome which was suspected because of the presence of the following clinical features: apparent typical facial appearance, microcephaly, dwarfism (last body weight 22 kg, last height 112 cm; there were no measures available for head circumference, arm span and lower and upper segments), and mild mental retardation [7]. Additionally, we found the patient to have a disproportionately short stature due to short limbs with truncal obesity, a poor dentition status with small teeth of which some were missing and with the remaining ones with mottled enamel and caries, and a prominent nose. Also, intrauterine growth failure was reported by the parents. He was known to have hypothyroidism, systolic hypertension, hypertriglyceridemia, hypercholesterolemia, and significantly reduced high-density lipoprotein cholesterol. A photograph of the patient was published by Seeburger et al. [7]. In synopsis of all diagnostic findings, we doubted the initial diagnosis of Dubowitz syndrome and consecutive genetic testing confirmed MOPD II. All of the clinical findings in our patient except the hypothyroidism, the lipid metabolism disorder, the history of myocardial infarction, and the systolic hypertension were consistent with this diagnosis. Genetic testing revealed two compound heterozygous mutations in the *pericentrin* (*PCNT*) gene inherited from healthy carrier parents (c.1388C > G (exon 9) and c.5767C > T (exon 28), both leading to a translational frameshift and premature stop codons (p.S463* und p.R1923*)).

Following transfemoral endovascular coiling (right-sided approach) of two aneurysms (Fig. 2, panels a and b), the

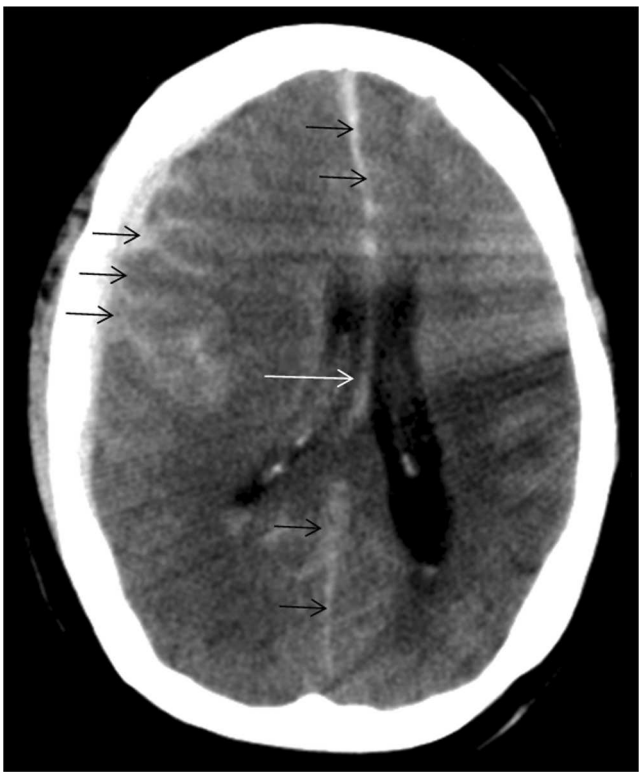

Fig. 1 Cranial computed tomographic scan on admission of the patient showing right-sided subarachnoidal hemorrhage (*left arrows*) with blood in the interhemispheric fissure (*central arrows*) and consecutive midline shift to the left (*white arrow*)

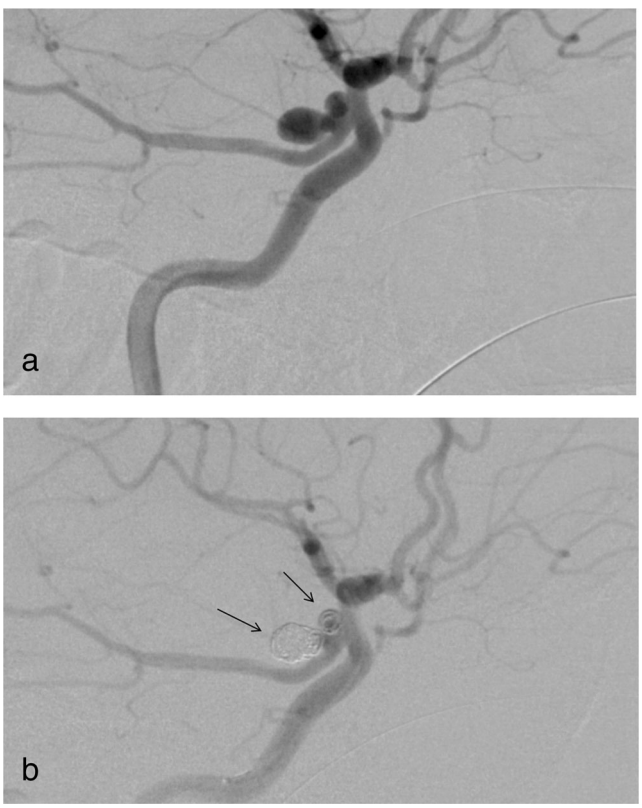

Fig. 2 Cerebral aneurysms of the right internal carotid artery (shown in panels **a** and **b**) occluded by multiple coils (*arrows in* **b**)

clinical convalescence after SAB was prolonged and intensive care treatment lasted as long as four weeks. The further clinical course was complicated by generalized arterial spasms, multiple thrombotic events, and long-term catecholamine therapy, all together leading to insufficient blood flow in the right leg. Attempts of interventional as well as surgical revascularization were unsuccessful; hence, right-sided transgenicular leg amputation became necessary. Circulatory deficiencies were also obvious in the remaining upper and lower extremities, and furthermore, electrocardiogram (ECG) showed recurrent ST-segment elevations with continuously elevated blood levels of cardiac enzymes. Cardiac catheterization showed poor left ventricular function and a hypoplastic coronary artery system (Fig. 3, panel a). Additionally, one of the bypass grafts showed thrombotic occlusion and the other one was found to be significantly obstructed (Fig. 3, panel b). Mutations in the *MTHFR* gene were discovered (homozygous for c.665C > T, heterozygous for c.1286A > C, OMIM: *607093) partially explaining cardiovascular complications. However, only limited treatment options were available and a conservative approach administering partial thromboplastin time (PTT)-controlled unfractionated heparin (PTT 40–50 s.) was chosen. In the clinical course, the patient developed pneumonia and broad-spectrum antibiotic treatment was required. Nevertheless, he became septic leading to cardiovascular depression and ventricular fibrillation. Cardiopulmonary resuscitation was effective with return of spontaneous circulation after a few minutes.

Intracranial pressure was elevated for the first weeks after SAB measured continuously by Codman intracranial pressure probe, so extraventricular drainage had to be established. Later on, post hemorrhaging hydrocephalus aresorptivus became evident and repeated predominantly right-sided seizures occurred despite antiepileptic treatment with levetiracetam.

After one month of intensive medical care, the patient was referred to a specialized rehabilitation center. At that time, he still required invasive ventilation and had not adequately regained consciousness after ending sedative measures. Some weeks later, the patient died due to rupture of another cerebral aneurysm.

Discussion

MOPD II is a genetic disorder caused by homozygous or compound heterozygous mutations in the *PCNT* gene on chromosome 21q22 [6]. Clinically, the syndrome was first delineated by Majewski et al., who reported on three unrelated children with intrauterine and postnatal dwarfism, facial features resembling those of Seckel syndrome, and disproportionate shortness of forearms and legs [3]. In a review of 58 individuals with MOPD II, Hall et al. reported that 19 % of the patients were found to have intracranial aneurysms [2]. Other vascular complications such as Moyamoya disease of the cerebral arteries or tortuous cerebral vessels and cardiac problems altogether entailing life-threatening complications were described as well [2, 5].

In our patient, the morphologic appearance in combination with mild mental retardation had led to the diagnosis of Dubowitz syndrome at a young age. Coronary artery narrowing or other vascular complications had not been described previously to be associated with this syndrome until Seeburger et al. assumed to have found a new feature of Dubowitz syndrome in the patient now diagnosed as having MOPD II [7].

Dubowitz syndrome was first described in 1965 in four patients with short stature, microcephaly, facial abnormalities, mild mental retardation, and eczema [1]. So far, no causative genetic abnormality is described. In a review of families with two or more affected family members, Opitz et al. assumed an autosomal recessive inheritance [4]. Vascular abnormalities have not been described previously in this syndrome.

In our patient, it is highly probable that the development of the cerebral aneurysms as well as of the coronary angiopathy

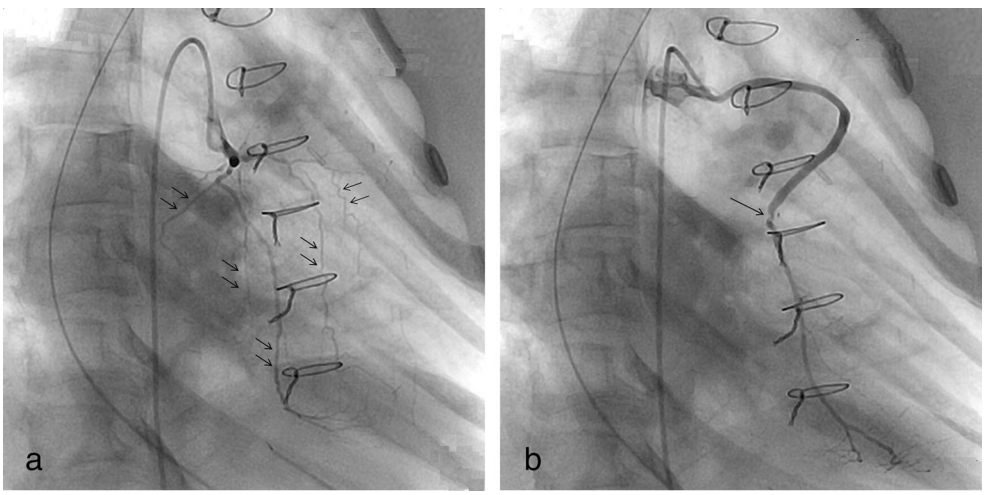

Fig. 3 Coronary angiography of the left coronary artery showing highly hypoplastic vessels (*arrows* in **a**) and significant narrowing of the venous aortocoronary bypass to the ramus circumflexus of the left coronary artery with significant distal stenosis (*arrow* in **b**)

was a result of the vascular changes on the basis of the mutation in the *PCNT* gene. It is likely that the cardiovascular problems were aggravated by the presence of a homozygous *MTHFR* mutation in this patient.

One can only speculate that earlier genetic testing and earlier diagnosis of MOPD II would have led to earlier cranial imaging and subsequently to preventive interventional treatment of the cerebral aneurysms. It remains unclear if this had improved the uncertain prognosis of this patient with severe coronary artery disease. However, finding a pattern of symptoms not typical for a well known syndrome (in our case Dubowitz syndrome) should always lead to reconsidering genetically testable conditions. Whenever mutations in the *PCNT* gene are detected in a patient with significant growth retardation, a full vascular status including cerebral imaging and cardiac evaluation needs to be determined as mortality is high due to cerebrovascular anomalies.

Conflict of interest The authors declare that they have no conflict of interest.

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